Draw Pharmacology in your mind

General Pharmacology

If you are a pharmacy student
If you are postgraduate and want to revise pharmacology by an easy way
If you are using any pharmacology reference
this file will aid you
> And wait for more <

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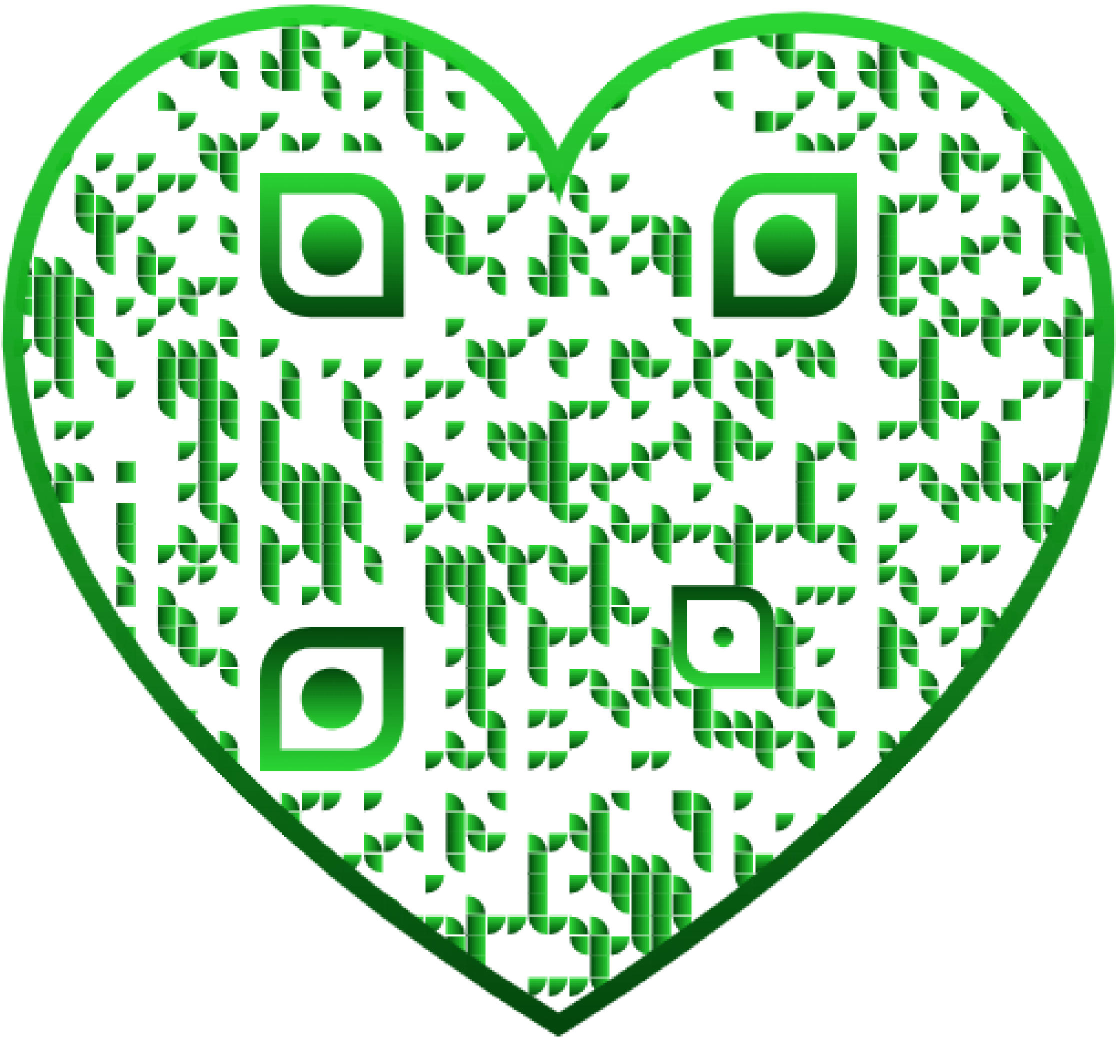

GENERAL PHARMACOLOGY

What is Pharmacology ?

It is the science that deals with the study of chemical substances (Drugs)

- What they are ? → Sources, Chemical & Physical properties
- How they work ? → Mechanism of actions , Side effects
- What they do ? → Biological effects , Therapeutic use, Pharmacokinetics and Pharmacodynamics .. etc

Drugs: any chemical substance that can affect living tissues and can be **used in diagnosis** , **prevention** or **treatment** of diseases

Sources of Drugs

- **Natural**
  - **Plant** ex. Digitalis Glycosides - atropine
  - **Animals** ex. Heparin - insulin
  - **Microorganisms** ex. Antibiotics (Penicillin)
  - **Minerals** ex. Ferrous Sulphate - Magnesium sulphate
- **Synthetic** ex. Sulphonamides
- **Semisynthetic** ex. Homatropine methyl bromide
- **Biosynthetic**
  - **Genetically engineered drugs**
  - ex. Recombinant DNA Human Insulin

the gene responsible for insulin synthesis is incorporated into genome of E.coli

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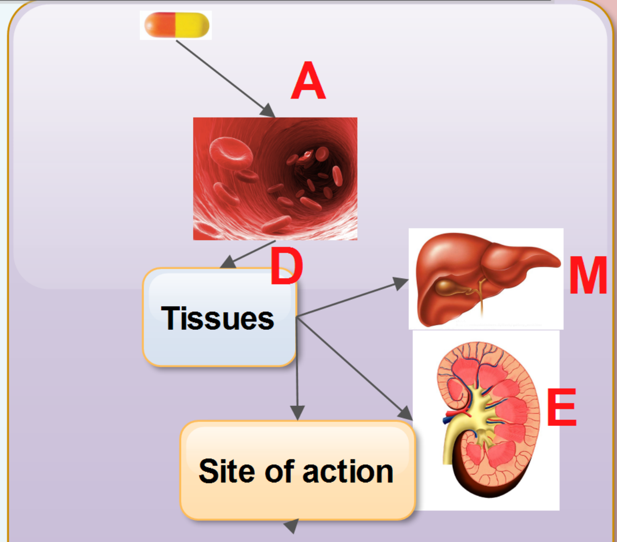
Divided to:

- **Pharmacokinetics** What the **BODY** does to the **DRUG** — **ADME**
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- **Pharmacodynamics** What the **DRUG** does to the **BODY** — Mechanism of action



Pharmacological effect = Clinical response

PHARMACODYNAMICS

How does the drug affect the body ? — **Through its action on**

- **Ion Channels**
- **Carriers**
- **Enzymes**
- **Receptors**
  - **What is ?**
  - **Types ?**
    - Channel-linked receptors / Ligand-gated ion channels
    - G-Protein coupled receptors
    - Enzyme-linked (Tyrosin kinase-linked) receptors
    - Nuclear receptors

Proteinaceous macromolecules exist mainly on cell surface and part of them may exist intracellular. They receive the drug, hormones or transmitter substances that occur naturally in the body --> Series of changes within the cell occur --> **and then that gives response** such as muscle contraction or relaxation, controlling glands secretion ... etc

Any drug or substance binds to the receptor activating or inactivating it is called **" Ligand "**

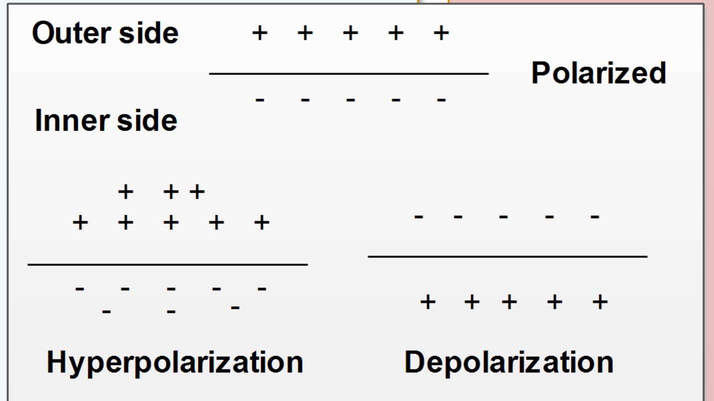


Figure (1)

We need first to know "Membrane Potential"

We have 4 main types of ions that manage the electricity in our body : **Na^+ , K^+ , Ca^{+2} , Cl^-**

Na^+ , Ca^{+2} and Cl^- at the outer side the cell membrane and **K^+ at the inner side** the cell membrane

In **Normal** state **(Resting membrane potential)** the membrane is **Polarized**
(+ve charge outside and -ve charge inside)

When **Na^+ or Ca^{+2} enters** in this case the membrane is **Depolarized "excitation"**

In case of **K^+ outflux or Cl^- influx** the membrane it makes outer side more +ve and inner side more -ve this is called **"Hyperpolarization" "inhibition"**

As illustrated in the figure (1)

Potency of the ligand depends on

Affinity

The ability of the drug to **BIND** to the receptor

Efficacy

Also called
" Intrinsic activity , Effectiveness "

The ability of the drug to **ACTIVATE** the receptor and **give response** after binding

Ligand types

Agonist

Binds to receptor and **produces response**

Produces a response that **mimics** the response produced by the **endogenous ligand**

Phenylephrine is an agonist at α1 receptor produces an effect similar to **noradrenaline** *(the endogenous ligand)*

Full agonist

High affinity Binds to receptor

Maximal response **High efficacy**

Acetylcholine Ach & Norepinephrine **Example**

Partial agonist

Binds to receptor **High affinity**

Intermediate efficacy (Gives certain **percentage** of biological response **but not maximal)** **Submaximal response**

Example Pindolol

Antagonist

Strongly binds to the receptor and produce **no response**

Strongly binds **Maximum affinity** Higher than agonist's affinity

No response, Block the receptor's effect **Zero efficacy**

Example Propranolol is a β receptor blocker --> prevent actions of Adrenaline

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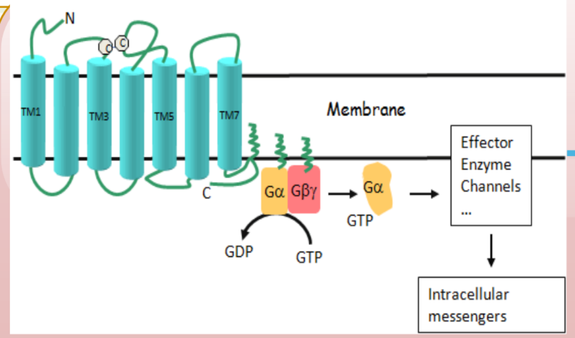


3 Subunits= α + β + γ +
a **GDP** molecule bound to α **subunit**

Start by the *"Channel-linked receptors"* in the next page then return to this page

Receptors Types Cont,

2. G-Protein coupled receptors

Called **Metabotropic**

Seconds Action in

Membrane receptors

Linked to **G-Protein**

Steps

1. **Agonist bind** to it's binding site on the receptor
2. The cytoplasmic domain of the receptor is altered to **fit α-GDP complex**
3. **GDP** in replaced by **GTP** which contain **energy**
4. α-GTP complex migrate to the **effector system**
5. response is generated through formation of **2ry messenger**
6. The response is sustained as long as the agonist (primary messenger) is in it's binding site and is terminated when it goes away.

Types of 2ry messenger

Adenylate cyclase / cAMP system

Effector

Adenylate cyclase
ATP → cAMP

2ry messenger

cAMP activates **protein kinase** phosphorylates (Enzymes ,Proteins ...etc)

Examples

Stimulation of β_1 receptor in the heart
→ cAMP production
→ activation of protein kinase
→ phosphorylation of Ca^{+2} channels
→ Ca^{+2} influx
→ increase force of contraction of the heart.

Stimulation of β_3 receptor in the liver
→ cAMP production
→ activation of protein kinase
→ phosphorylation/ activation of enzymes responible for glycogenolysis and lipolysis
→ glycogen and fat catabolism

Phospholipase C (PLC) / inositol triphosphate system

Effector **PLC**

Catalyze hydrolysis of **phosphoinositol diphosphate PIP_2** (a membrane phospholipid constituent) to **two 2ry messengers**

2ry messengers

Inositol triphosphate (IP_3)
→ binds to endoplasmic reticulum protein
→ release Ca^{+2} from intracellular stores
→ Ca^{+2} increase
→ muscle contraction , secretion from exocrine glands .. etc

Diacylglycerol (DAG)
→ activates *protein kinase C*
→ phosphorylation of other proteins and enzymes → responce

Ion Channels

G-Protein coupled receptors can **control ion channels directly without involving 2ry messenger**

ex. M_2 receptors in cardiac muscle
→ increase K^+ outflux
→ hyperpolarization
→ relaxation

Examples of G-protein coupled rec.

Dopaminergic receptors

Muscarinic Ach receptors

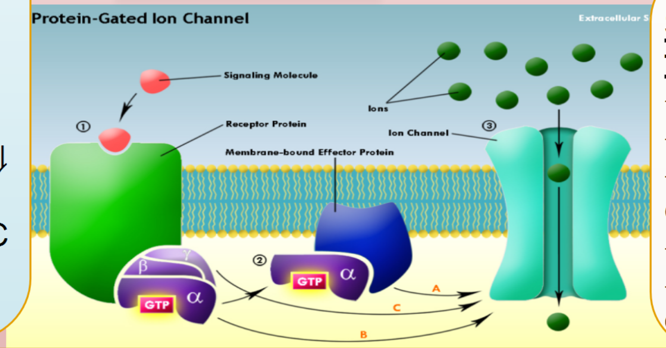
Opiate receptors

α & β adrenoceptors

Serotonin receptors

So G-Protein receptors are classified to:

G_s : Stimulate adenylyl cyclase
→ ⇑ **cAMP**
G_i : Inhibit adenylyl cyclase → ⇓ **cAMP** / open K^+ channel
G_q : Stimulate phospholipase C
→ ⇑ **IP_3 & DAG**
G_0 : Closes Ca^{+2} Channels



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Receptors Types Cont,

3. Enzyme-linked (Tyrosin kinase-linked) receptors

Membrane receptors

Effector domain (Cytoplasmic domain)

Contain an **enzyme** as a part of their structures

Mostly "Tyrosine kinase"

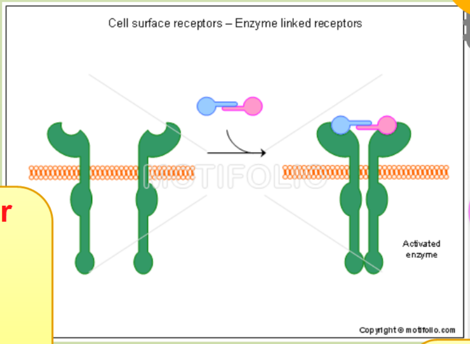
Other enzymes
Serine Kinase , Threonine Kinase and Guanylyl cyclase

Mechanism

→When the agonist binds to the receptor
→ assembly of **two** receptors to form dimer
→activates ***tyrosine kinase***
→Leading to *phosphorylation of tyrosine residue* in the receptor and on other specific segnalling proteins
→ *final response*

Examples

1. **Insulin receptor**
2. **Epidermal growth factor receptors**
3. **Growth hormone receptors**


Cell surface receptors – Enzyme linked receptors
Activated enzyme
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1. Channel-linked receptors / Ligand-gated ion channels

Called also **Ionotropic**

Membrane receptors

Linked to ion channels

So, they are responsible for opening the channel when activated --> flow of ions --> response

Synaptic transmission — **Milliseconds**

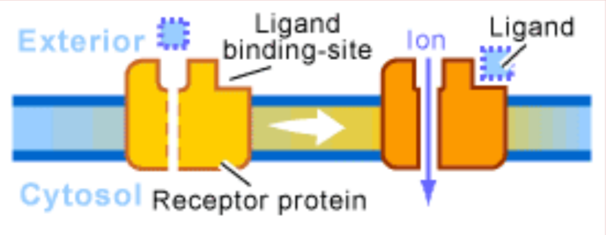
Examples

GABA$_A$ receptors

-When GABA binds to it's receptor
-The Cl^- channels open leading to influx of the Cl^- ions
-Leading to hyperpolarization of the cell membrane

Nicotinic receptors

-When Ach binds to it's receptor
-The Na^+ channels open leading to influx of Na^+ ions
-So depolarization of the cell membrane occurs


Exterior
Ligand binding-site
Ion
Ligand
Cytosol
Receptor protein

4. Nuclear receptors

Intracellular receptors

Very slow in action

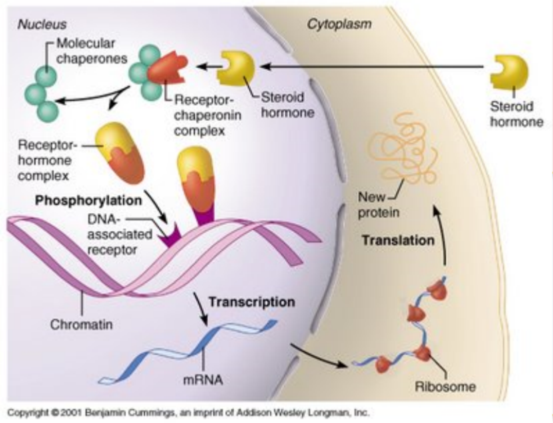
So, the agonist must enter the cell to reach the
Highly lipophilic

Their action is obtained through **synthesis** of new **proteins** or **enzymes**

Activation of nuclear receptors → transcription of DNA → mRNA → Protein synthesis → response

Examples

1. **Steroidal hormone receptors**
2. **Vitamin D receptors**
3. **Thyroid receptors**


Nucleus
Cytoplasm
Molecular chaperones
Receptor-chaperonin complex
Steroid hormone
Steroid hormone
Receptor-hormone complex
Phosphorylation
DNA-associated receptor
Chromatin
Transcription
mRNA
New protein
Translation
Ribosome
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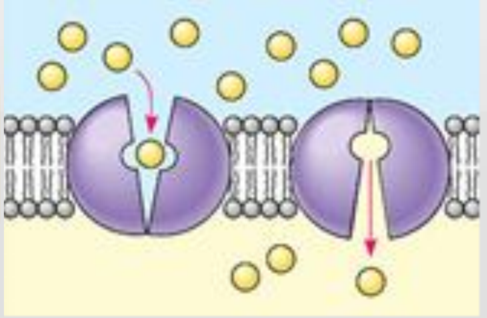
Now we have just finished talking about "Receptors" .. look back "Carriers" , "Enzymes" , "Ion channels" are left, So let's talk about

Carriers

What is ? — **Proteins**

What they do ?

Polar molecules could not just pass through the phospholipid membrane, so they need **"carrier"** that helps them moving across the cell membrane **(Small organic molecules and ions)**



Examples for the carriers

The carriers which are responsible for
1. Transporting **glucose** and **aminoacids into** cell
2. Transporting **Na^+ and Ca^{+2} ions out** of cell
3. Reuptake of neurotransmitters

Examples of drugs targeting carriers

1. **Proton Pump Inhibitors "PPIs" (ex. Omeprazole)** which inhibit **H^+/K^+ ATPase pump** which is responsible for transporting of H^+ against concentration gradiant in stomach
2. **Tricyclic antidepressants "TCAs"** inhibit the **reuptake of noradrenaline**

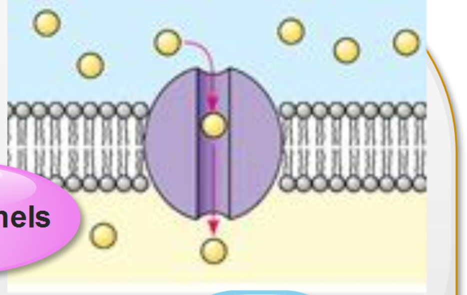
Enzymes

Enzymes can be the target of a certain drug, so the drug inhibit the enzyme's activity

Examples

1. Irreversible inhibition of **cyclooxygenase enzyme COX** enzymes by **Aspirin**
2. Reversible inhibition of **cholinestrase enzyme** by **neostigmine**

Ion Channels



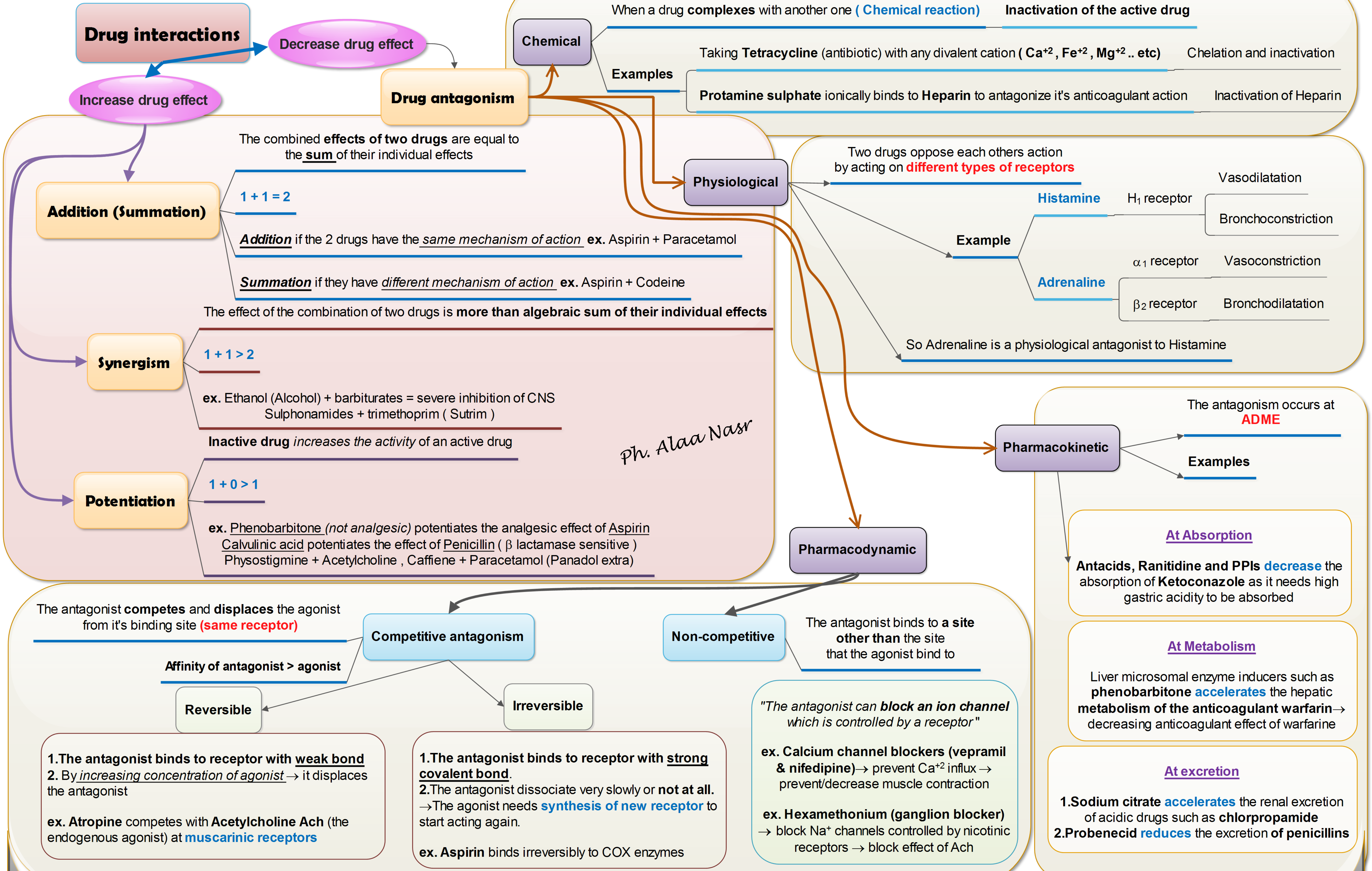
They are **transmembrane pores surrounded by protein subunits**

2 types

Self-operated channels (Direct channels)

Serves as **direct target for the drug (Voltage gated Na^+ , Ca^{+2} , K^+ , Cl^- channels)** → Change voltage across the cell membrane

Receptor-operated channels
(linked to receptors)



Drug interactions

Increase drug effect

Addition (Summation)

The combined **effects of two drugs** are equal to the **sum** of their individual effects

1 + 1 = 2

Addition if the 2 drugs have the *same mechanism of action* **ex.** Aspirin + Paracetamol

Summation if they have *different mechanism of action* **ex.** Aspirin + Codeine

Synergism

The effect of the combination of two drugs is **more than algebraic sum of their individual effects**

1 + 1 > 2

ex. Ethanol (Alcohol) + barbiturates = severe inhibition of CNS
Sulphonamides + trimethoprim (Sutrim)

Potentiation

Inactive drug *increases the activity* of an active drug

1 + 0 > 1

ex. Phenobarbitone *(not analgesic)* potentiates the analgesic effect of Aspirin
Calvulinic acid potentiates the effect of Penicillin (β lactamase sensitive)
Physostigmine + Acetylcholine , Caffiene + Paracetamol (Panadol extra)

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Decrease drug effect

Drug antagonism

Chemical

When a drug **complexes** with another one **(Chemical reaction)** — **Inactivation of the active drug**

Examples

- Taking **Tetracycline** (antibiotic) with any divalent cation **(Ca^{+2} , Fe^{+2} , Mg^{+2} .. etc)** — Chelation and inactivation
- **Protamine sulphate** ionically binds to **Heparin** to antagonize it's anticoagulant action — Inactivation of Heparin

Physiological

Two drugs oppose each others action by acting on **different types of receptors**

Example

- **Histamine**
  - H_1 receptor — Vasodilatation
  - Bronchoconstriction
- **Adrenaline**
  - α_1 receptor — Vasoconstriction
  - β_2 receptor — Bronchodilatation

So Adrenaline is a physiological antagonist to Histamine

Pharmacokinetic

The antagonism occurs at **ADME**

Examples

At Absorption

Antacids, Ranitidine and PPIs decrease the absorption of **Ketoconazole** as it needs high gastric acidity to be absorbed

At Metabolism

Liver microsomal enzyme inducers such as **phenobarbitone accelerates** the hepatic **metabolism of the anticoagulant warfarin**→ decreasing anticoagulant effect of warfarine

At excretion

1.Sodium citrate accelerates the renal excretion of acidic drugs such as **chlorpropamide**
2.Probenecid reduces the excretion **of penicillins**

Pharmacodynamic

Competitive antagonism

The antagonist **competes** and **displaces** the agonist from it's binding site **(same receptor)**

Affinity of antagonist > agonist

Reversible

1.The antagonist binds to receptor with weak bond
2. By *increasing concentration of agonist* → it displaces the antagonist

ex. Atropine competes with **Acetylcholine Ach** (the endogenous agonist) at **muscarinic receptors**

Irreversible

1.The antagonist binds to receptor with strong covalent bond.
2.The antagonist dissociate very slowly or **not at all.**
→The agonist needs **synthesis of new receptor** to start acting again.

ex. Aspirin binds irreversibly to COX enzymes

Non-competitive

The antagonist binds to **a site other than** the site that the agonist bind to

*"The antagonist can **block an ion channel** which is controlled by a receptor"*

ex. Calcium channel blockers (vepramil & nifedipine)→ prevent Ca^{+2} influx → prevent/decrease muscle contraction

ex. Hexamethonium (ganglion blocker) → block Na^+ channels controlled by nicotinic receptors → block effect of Ach

PHARMACOKYNETICS

As we said **"What the BODY does to the DRUG"**

It is summarized in ADME

Absorption

Distribution

Metabolism

Excretion

The transfer of the drug from the site of administration to the systemic circulation

Drug have to pass through **barriers** to reach circulation

1. **GIT wall** - if applied orally
2. **Skin** - if applied topically
3. **Blood Brain Barrier (BBB)** - if it is intended to reach CNS
4. Capillaries' walls .. etc

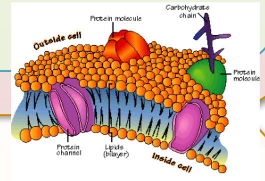
CELL MEMBRANE

We need to know that

1- Cell membrane consists of **phospholipid bilayer** with embedded proteins → lipid in nature → allow lipid soluble *(lipophilic)* molecules to pass through it

so, *the drug must have a certain degree of lipid solubility to pass through the cell membrane easily*

2- What about lipid insoluble molecules?
cell membranes have pores/channels that allow lipid insoluble molecules of small dimensions to pass



Drug passage through barriers
Cell membranes

1. Passive (simple) diffusion

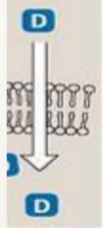
Concentration gradiant — Driving force

Passage from **HIGH concentration to LOW** concentration

Simple lipid diffusion

For **lipid soluble** drugs (lipophilic)

No energy is required — **Parallel to Concentration gradient**



Can't be saturated

Can't be inhibited by other substance

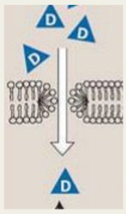
No carriers are required

Simple aqueous diffusion

For **lipid insoluble** drugs of small sizes **(Hydrophilic)**

No energy — **Parallel to Concentration gradient**

Passage of the drug occurs through

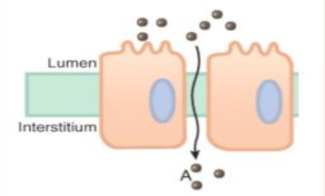


Passage through pores

Aqueous channels in cell membrane

For small size molecules dissolved in water

Paracellular transport



Through **intracellular gaps**

Filtration : passage of *large amount* of solvent together with substance dissolved in it *through **pores** in the cell membrane*
ex. Glomerular filtration in the kidney
→Filtration requires **wide pores** in the cell membrane and **high pressure**

2. Specialized transport

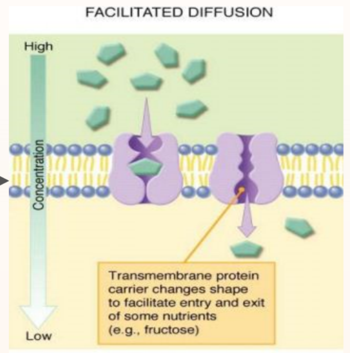
Facilitated diffusion

Parallel to concentration gradient — **High to low**

Carrier is needed — Can be **saturated** and **inhibited**

No energy is required

ex. Fructose transport


FACILITATED DIFFUSION
High
Concentration
Low
Transmembrane protein carrier changes shape to facilitate entry and exit of some nutrients (e.g., fructose)

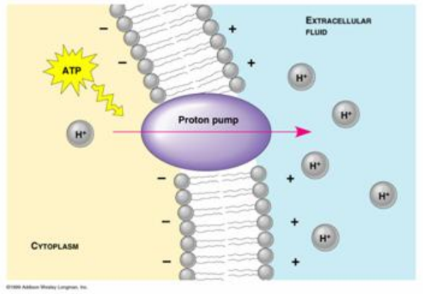
Active transport

Against concentration gradient — **Low to high**

so, Energy is utilized

Carrier is needed — Can be **saturated** and **inhibited by competitors**

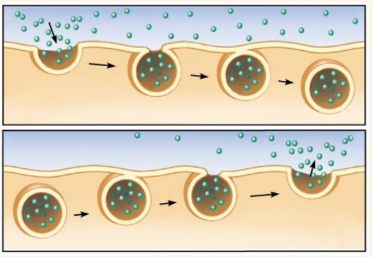
ex.Uptake of glucose into the cells is mediated **by *facilitated diffusion* and *active transport***



Endocytosis

For **lipid insoluble**, **LARGE** size molecules

Engulfment of the drug molecule / extracellular substance by cell membrane into small vesicle that releases its contents *inside the cell or extruded from the other side of the membrane*



Energy is utilized

Types

- **Phagocytosis** — Engulfment of **solid** particles
- **Pinocytosis** — Engulfment of **the extracellular fluid**
- **Receptor-specific endocytosis**
  - ex. GIT absorption of **(Vit B12+intrinsic factor** complex) — Vit B_{12} binds to intrinsic factor
  - **Iron intake by RBCs** — Iron binds to transferrin

Deficiency of intrinsic factor ⇓ oral absorption of vit B_{12} → treated by vit B_{12} injections

→Endocytosis of intrinsic factor and its receptor in GIT

→Endocytosis of transferrin and its receptor on RBCs

Exocytosis

Secretion of substances from the cell by the same mechanism
***ex.** Release of neurotransmitters as Ach and noradrenaline*

Factors affecting passive diffusion

1. PH of the medium and polarity of drugs

Most drugs are *weak electrolytes*

Present as *ionized* and *unionized* forms

To cross the cell membrane the drug must be *more lipid soluble*

✓ Unionized

Remember
ionized form = have a + or - charge = water soluble
unionized form = NO charge = lipid soluble

This is controlled by

Handerson-Hasselbalch equation

PKa = PH + Log (protonated form) / (unprotonated form)

For weak acids

ex. Salicylates and Barbiturates

PKa = PH + Log (Unionized / ionized)

$RCOOH \rightleftarrows RCOO^- + H^+$

Let's use our brains

In the acidic medium of stomach (PH 1.4)
→ "There would be excess H^+" *see the reaction*
→ So, the reaction is shifted to the left
→ ⇑ **unionized form**
"More lipid soluble"
→ absorbed from the stomach to the plasma

In the more alkaline medium of plasma (PH 6.4)
→ the reaction is shifted to the right
→ ⇑ **ionized form**
"More lipid insoluble"
→ Trapped the plasma and don't return back to stomach

For weak bases

ex. ephedrine , morphine , strychnine

PKa = PH + Log (ionized / unionized)

$RNH_3^+ \rightleftarrows RNH_2 + H^+$

Let's use our brains

In the acidic medium of stomach (PH 1.4)
→ "There would be excess H^+" *see the reaction*
→ So, the reaction is shifted to the left
→ ⇑ **ionized form**
"More lipid insoluble"
→ NOT absorbed from the stomach

When the drug reaches the alkaline medium of the intestine (PH 7-8)
→ the reaction is shifted to the right
→ ⇑ **unionized form**
"More lipid soluble"
→ absorbed from intestine

For Strong bases

ex. d-tubocurarine

Strong bases have **high PKa** (ex.10)

So, the drug presents in **ionized form**

NOT absorbed from the whole GIT

So, NOT given orally

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2. Available surface area

Stomach is not the major site of absorption (EVEN ACIDIC DRUGs) !!! **WHY !**

Surface area of stomach is **small**

Gastric epithelium is **lined with sick mucous layer**

Intestine is the major site for absorption of acidic and basic drugs **WHY !**

Surface area of the intestine is **large** (1000 times more than the stomach)

Intestinal epithelium is **NOT lined by thick mucous layer**

3. Blood flow

Blood flow to the intestine **>** Blood flow to the stomach

So, Absorption from intestine is **>** absorption from stomach

4. Binding of the drug to plasma proteins

Cell membrane is permeable to the drug in the free form

When the drug is strongly bound to plasma proteins

Absorption increase

The drug passes from GIT to plasma → attach to plasma proteins → No return → increase absorption

Remember
PH + POH = 14
PKa + Pkb = 14

PKa is the PH at which *ionized form = unionized form*

Passive flux / diffusion according to concentration gradient is governed by

Fick's law of diffusion

Flux = [Concentration gradient (C_1-C_2) X Area X Permeability coefficient**] /** Thickness

Permeability coefficient

Measures the **mobility** of the drug

Depends on **lipid solubility** "Partition coefficient)

So, ⇑ lipid solubility (lipophilicity) → ⇑ permeability coefficient → ⇑ passage of the drug

So, Flux (amount of the drug that passes through the cell membrane)

Directly proportional to
- Concentration gradient
- Surface area of cell membrane
- Permeability coefficient

Inversely proportional to
- Thickness of cell membrane

Routes of drug administration

1. Oral (enteral) administration

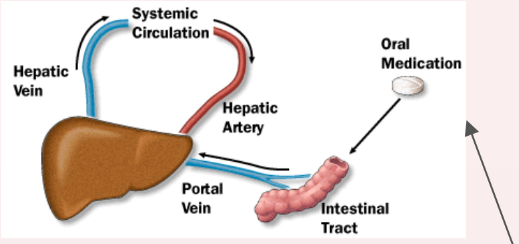
- The most convenient route
- Absorption depends on **lipid solubility "partition coefficient"** of the drug
- *Lipophilic drugs "unionized form"* are well absobed orally
- Absorbed by *passive diffusion*

Factors affecting oral absorption

- PH of the medium and polarity of the drug ✓
- Surface area of absorption ✓
- Blood flow ✓
- Plasma protein binding ✓
- **Gastric emptying rate**
  - *Sympathetic* stimulation + presence of *food* in the stomach
    - ***Delay gastric emptying***
      - ***Inactivation of the drug in the stomach***
      - ***Decrease absorption of drugs***
  - **In case of diarrhea** → ⇑ **GIT emptying** → ⇓ contact time → ⇓ absorption

Drugs not suitable for oral administration

- *Totally lipophilic* drugs
- *Highly hydrophilic* drugs
  - ex. Hexamethonium
- Drugs *destroyed by gastric acidity*
  - ex. Penicillin G
- Drugs affected by **first pass effect**
  - ***Metabolism*** *of the drug before it reaches systemic circulation* ***by :***
    - ***Digestive enzymes*** – ex. Insulin
    - ***Enzymes in gut wall***
    - ***Bacterial enzymes***
    - ***Hepatic enzymes***
  - Can be compensated by **increasing the dose** if the metabolites are safe
    - ⇑ dose — 60 - 75 % affected — ex. Propranolol
  - **ibutilide** "anti-arrhythmic drug" undergoes *extensive first pass effect* → NOT given orally → used **IV** only



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2. Sublingual

- Higher concentration of the drug
  - Absorption from oral mucosa is **rapid**
    - ***High blood flow***
  - **No first pass effect**
- **ex. Nitroglycerin**
  - Extensive hepatic first pass effect
  - Oral bioavailability = Zero
  - So, not given orally

3. Rectal

- Useful mainly in **unconscious patients** and in **vomiting**
- Reduced hepatic first pass effect — 50% less than oral

4. Parenteral

- ***Intravenous IV***
  - **Very rapid in action** but High probability to cause **toxicity**
  - **Lipid insoluble** drugs mainly given by
    - ***absorbed through pores / aqueous channels*** in the endothelium of the blood vessels
- **Lipid soluble** drugs mainly given by
  - ***Intramuscular IM***
  - ***Subcutaneous SC***
    - Used to produce **sustained release** (because of *lowblood supply* to SC tissue)
      - ex. Insulin
      - ex. Contraceptives
        - Pellets implanted SC for 3 years ex. Nexplanon , implanon
  - ***absorbed by simple diffusion***
- **Large molecules (ex. proteins)**
  - gain access to the blood through **lymphatic channels** or by **phagocytosis**

5. Pulmonary

- **Drugs given by inhalation**
  - **10%** reach respiratory tract
  - **90%** ingested in GIT
- **Systemic effect**
  - *Rapid entry to the blood due to*
    - ⇑ Surface area
    - ⇑ Blood supply
  - **ex.** Volatile anesthetics
- **Local effect**
  - **Aerosols** for *local effect on respiratory tract*
  - **ex.** Salbutamol (β_2 receptor stimulant → bronchodilatation)
    Cromoglycate (mast cell stabilizer)

6. Transdermal

7. Intranasal

8. Topical

Routes of drug administration

- Oral (enteral) administration ✓
- Sublingual ✓
- Rectal ✓
- Parenteral ✓
- Pulmonary ✓
- 6. Transdermal
- 7. Topical
- 8. Intranasal

6. Transdermal

For systemic effect

Transdermal administration

- Drugs can be *applied on the skin* **"transdermal patch"** – Absorbed to reach systemic circulation
- Provides a ***sustained effect***
- **The epidermis is a lipid barrier** – So, transdermal administration is used only for ***lipid soluble drugs***
- **Dermis is freely permeable to drugs**

Take care
Absorption of drugs is increased through abraded or denuded skin

ex. Nitroglycerine patches
Contraceptive patches (Ortho evra)

7. Topical

For local effect

Drugs can be applied on

- Skin
- Mucous membranes – Conjunctiva , Oropharynx , Colon , Urinary bladder , Vagina

8. Intranasal

Local effect

ex. Nasal decongestant sprays and drops

Systemic effect

For drugs which are *extensively affected by first pass effect* or **poorly absorbed orally**

ex. Vasopressin (ADH) or Desmopressin used in treatment of *diabetes insipidus*

Drug interactions at absorption site

Occurs when the patient takes **more than one drug** at the same time

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Reduced drug solubility

ex. Absorption of **Ketoconazole** (antifungal) is reduced by antacids , H_2 blockers as Ranitidine and PPIs

Formation of non-absorbable complex

ex. Fluoroquinolones as Ciprofloxacin (antibiotic) + Ca^{+2} or Fe^{+2} → **insoluble complex**

ex. Tetracyclines + Ca^{+2} *or any divalent cation* → **insoluble complex**

ex. Cholestyramine (bile acid-sequestering resin) can **bind to** Warfarin or Phenobarbital

Rapid emptying of the GIT

ex. Laxatives as $MgSO_4$ → ⇓ **Contact time** between the drug and it's absorbing surface → ⇓ **absorption** of other drugs

Reduced GIT motility

ex. Atropine and **Ganglion blockers** → ⇓ the **motility of GIT** → ⇓ delivery of drugs to their absorbing surfaces → inactivation of other drugs

PHARMACOKYNETICS

- **A**bsorption ✓
- **D**istribution
- **M**etabolism
- **E**xcretion

Distribution

Introduction

Drug can be distributed to "any or all" of (Plasma 4 litres - Interstitial fluids 10 litres - Intracellular fluids 28 litres **)**

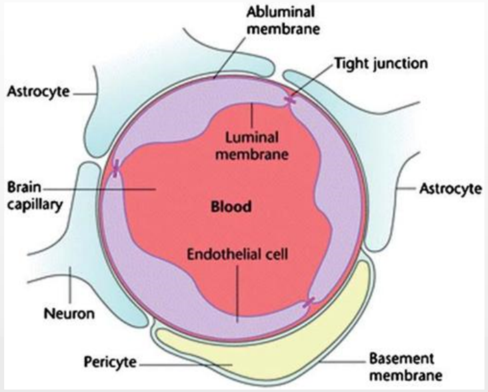
To reach the site of action *the drug must pass through several barriers such as* **Capillary wall**

- **Lipid soluble drugs** pass through **capillary endothelium**
- **Lipid insoluble drugs** pass through **capillary pores**
- **Large lipid insoluble drugs** as dextran are NOT distributed **stay in the plasma So, used as plasma substitute**

PHARMACOKYNETICS

- Absorption ✓
- Distribution
  - Introduction ✓
  - Factors contributing to unequal distribution of drugs
- Excretion
- Metabolism

5. Blood brain barrier BBB



BBB is a **membrane** that **encapsulates** and **protect CNS**

Capillaries of CNS are enveloped by **glial cells** *(astrocytes)*

Endothelial cells of capillaries and glial cells are connected together by tight junctions

BBB does not contain pores

Take care
- There is **NO aqueous diffusion *(no paracellular transport)*** across BBB → *ONLY lipid diffusion*
- **Amino acids** gain access to the brain through **carrier**

So, BBB is only permeable to lipid soluble compounds
ex. General anesthetics

But not permeable to hydrophilic substances

Glial cells
- Non-neuronal cells that surround neurons
- Hold neurons in place and supply nutrients and oxygen

1. Binding to plasma proteins

Are *high Mwt proteins present* in plasma as **albumin** and **globulin**

Some drugs tend to *bind to plasma proteins* **(become inactive)** and are *dissociated* after a while from them **to be active**

Some drugs are *strongly bound to plasma proteins*
ex. **Phenyl butazone** - **Coumarin**

Other drugs occur mainly *in free state*. **ex.** **antipyrine**

Take care
- Cell membrane is **only permeable** to drugs in the free form
- **Free drug** has pharmacological actions and can be metabolized and excreted
- **Protein bound drug** is NOT active , NOT metabolized , NOT excreted

Consequences of drug binding to plasma proteins

- Concentration of the *drug in the blood > in tissues*
- Protein bound drug acts as **depot / reservoir** → when free drug ⇓ → bound drug dissociates from plasma proteins to become free → Active
- **Increase half life** of drug (Not metabolized nor excreted)
- In case of **toxicity or hypersensitivity** manifestations will *take long time to disappear*

- *In case of hypoalbuminemia (albumin deficiency)* → ⇑ **free drug** → toxic manifestations may appear
- *When two highly protein bound drugs are given together* → ⇑ **free drug for both** → ⇑ therapeutic effect , toxicity and duration of action of both

Drug interactions at protein binding sites

Drugs with **high affinity** for binding to plasma proteins **displace** drugs with **lower affinity**

ex. Simvastatin , Clofibrate , Phenylbutazone → displace **Coumarin** (anticoagulant) → ⇑ free coumarin → bleeding

ex. Salicylates → displace **Tolbutamide** (hypoglycemic) → ⇑ free tolbutamide → hypoglycemic shock

4. Concentration in body fat

Storage in body fats occurs with **highly lipid soluble** drugs

ex. Thiopental , estrogen

2. Blood flow

As the blood flow is ⇑ to certain organ → it receives ⇑ amount of drug

Highly perfused organs
ex. Brain , Kidney , Liver
Receive **high** amount of drugs

Poorly perfused organs
ex. Fat , Tendons, Nails
Receive **low** amount of drugs

3. Cellular binding *(Preferential accumulation)*

Some drugs have *affinity for particular constituent of tissues*

So, the drug preferentially accumulate in these tissues

ex. *Chlorpromazine* accumulated in → Brain
Tetracyclines and metals → Bone & Teeth
Iodine → Thyroid gland (Specialized transport)
Digoxine → Heart , Kidneys , Liver
Arsenic → Keratin

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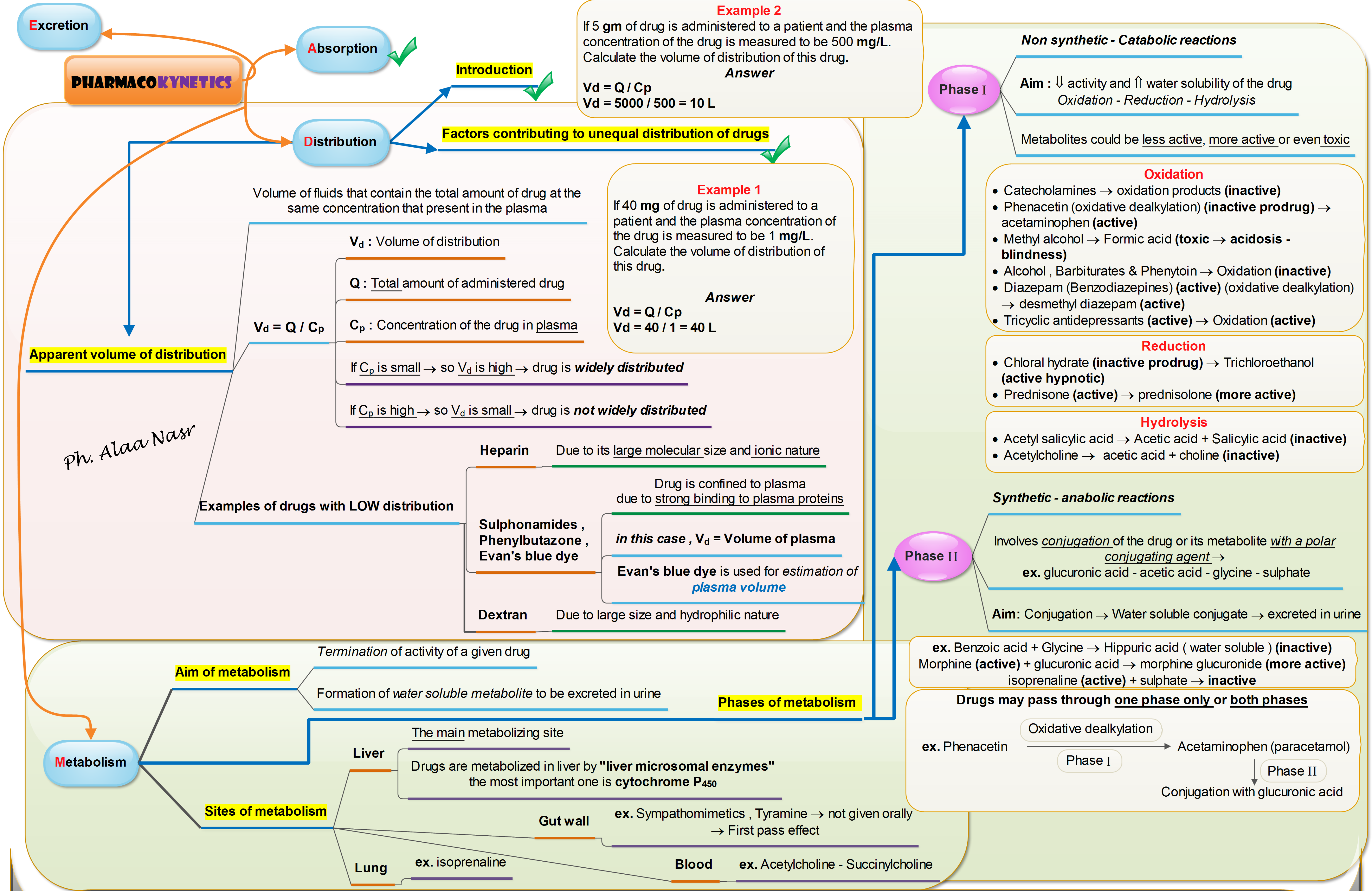

PHARMACOKYNETICS

Excretion

Absorption ✓

Distribution

- Introduction ✓
- Factors contributing to unequal distribution of drugs ✓
- **Apparent volume of distribution**
  - Volume of fluids that contain the total amount of drug at the same concentration that present in the plasma
  - **$V_d = Q / C_p$**
    - **V_d :** Volume of distribution
    - **Q :** Total amount of administered drug
    - **C_p :** Concentration of the drug in plasma
    - If C_p is small → so V_d is high → drug is ***widely distributed***
    - If C_p is high → so V_d is small → drug is ***not widely distributed***
  - **Examples of drugs with LOW distribution**
    - **Heparin** — Due to its large molecular size and ionic nature
    - **Sulphonamides , Phenylbutazone , Evan's blue dye** — Drug is confined to plasma due to strong binding to plasma proteins
      - ***in this case* , V_d = Volume of plasma**
      - **Evan's blue dye** is used for *estimation of* ***plasma volume***
    - **Dextran** — Due to large size and hydrophilic nature

Example 1

If 40 **mg** of drug is administered to a patient and the plasma concentration of the drug is measured to be 1 **mg/L**. Calculate the volume of distribution of this drug.

Answer

$V_d = Q / C_p$

$V_d = 40 / 1 = 40$ L

Example 2

If 5 **gm** of drug is administered to a patient and the plasma concentration of the drug is measured to be 500 **mg/L**. Calculate the volume of distribution of this drug.

Answer

$V_d = Q / C_p$

$V_d = 5000 / 500 = 10$ L

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Metabolism

- **Aim of metabolism**
  - *Termination* of activity of a given drug
  - Formation of *water soluble metabolite* to be excreted in urine
- **Phases of metabolism**
  - **Phase I** — ***Non synthetic - Catabolic reactions***
    - **Aim :** ⇓ activity and ⇑ water solubility of the drug
      Oxidation - Reduction - Hydrolysis
    - Metabolites could be less active, more active or even toxic
  - **Phase II** — ***Synthetic - anabolic reactions***
    - Involves *conjugation* of the drug or its metabolite *with a polar conjugating agent* →
      ex. glucuronic acid - acetic acid - glycine - sulphate
    - **Aim:** Conjugation → Water soluble conjugate → excreted in urine
- **Sites of metabolism**
  - **Liver**
    - The main metabolizing site
    - Drugs are metabolized in liver by **"liver microsomal enzymes"** the most important one is **cytochrome P_{450}**
  - **Gut wall** — **ex.** Sympathomimetics , Tyramine → not given orally → First pass effect
  - **Lung** — **ex.** isoprenaline
  - **Blood** — **ex.** Acetylcholine - Succinylcholine

Oxidation

- Catecholamines → oxidation products **(inactive)**
- Phenacetin (oxidative dealkylation) **(inactive prodrug)** → acetaminophen **(active)**
- Methyl alcohol → Formic acid **(toxic → acidosis - blindness)**
- Alcohol , Barbiturates & Phenytoin → Oxidation **(inactive)**
- Diazepam (Benzodiazepines) **(active)** (oxidative dealkylation) → desmethyl diazepam **(active)**
- Tricyclic antidepressants **(active)** → Oxidation **(active)**

Reduction

- Chloral hydrate **(inactive prodrug)** → Trichloroethanol **(active hypnotic)**
- Prednisone **(active)** → prednisolone **(more active)**

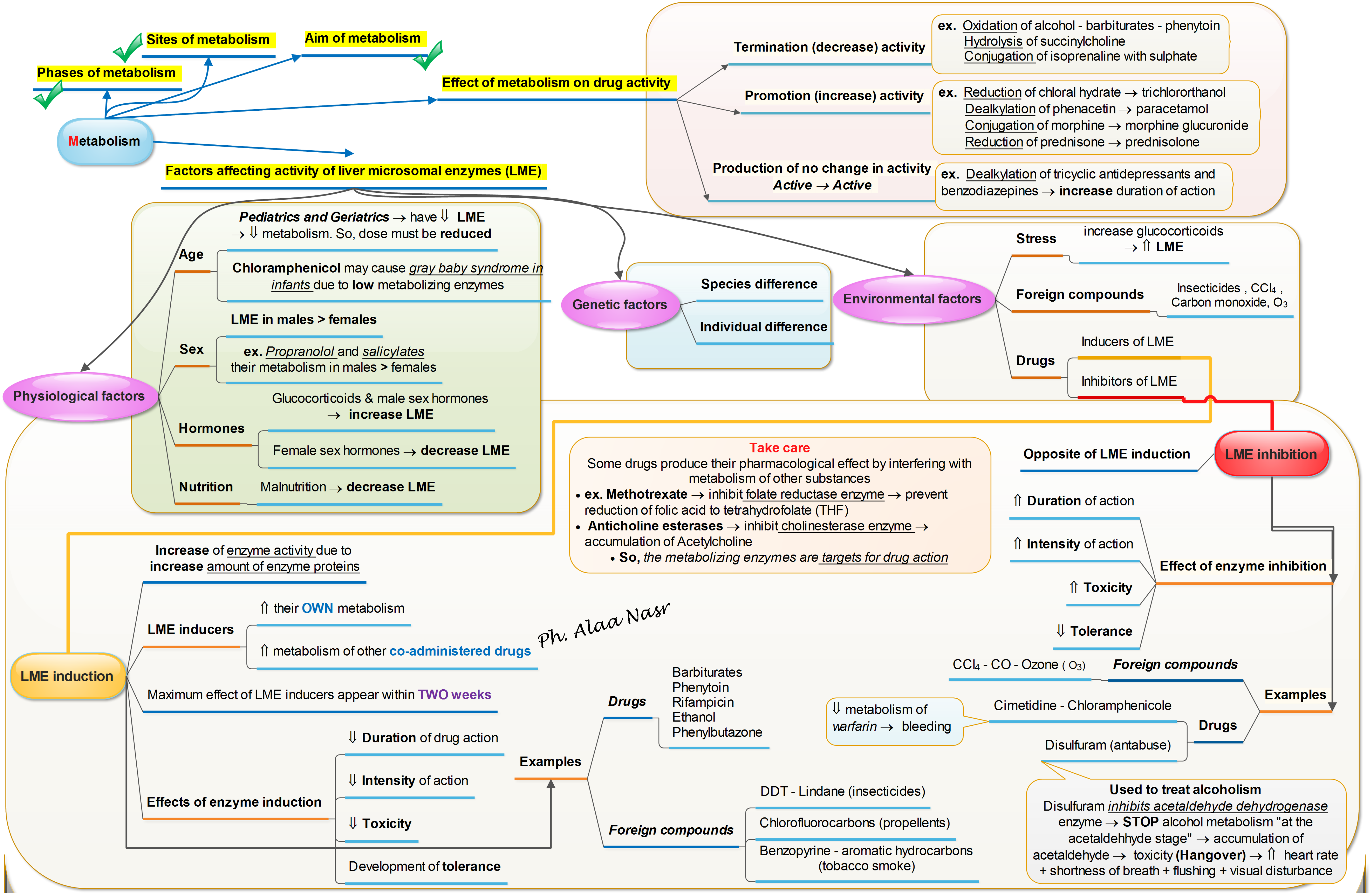
Hydrolysis

- Acetyl salicylic acid → Acetic acid + Salicylic acid **(inactive)**
- Acetylcholine → acetic acid + choline **(inactive)**

ex. Benzoic acid + Glycine → Hippuric acid (water soluble) **(inactive)**
Morphine **(active)** + glucuronic acid → morphine glucuronide **(more active)**
isoprenaline **(active)** + sulphate → **inactive**

Drugs may pass through one phase only or both phases

ex. Phenacetin —Oxidative dealkylation / Phase I→ Acetaminophen (paracetamol) —Phase II→ Conjugation with glucuronic acid



Metabolism
- Phases of metabolism ✓
- Sites of metabolism ✓
- Aim of metabolism ✓
- **Effect of metabolism on drug activity**
  - **Termination (decrease) activity**
    - **ex.** Oxidation of alcohol - barbiturates - phenytoin
    - Hydrolysis of succinylcholine
    - Conjugation of isoprenaline with sulphate
  - **Promotion (increase) activity**
    - **ex.** Reduction of chloral hydrate → trichlororthanol
    - Dealkylation of phenacetin → paracetamol
    - Conjugation of morphine → morphine glucuronide
    - Reduction of prednisone → prednisolone
  - **Production of no change in activity**
    Active → Active
    - **ex.** Dealkylation of tricyclic antidepressants and benzodiazepines → **increase** duration of action
- **Factors affecting activity of liver microsomal enzymes (LME)**
  - **Physiological factors**
    - **Age**
      - ***Pediatrics and Geriatrics*** → have ⇓ **LME** → ⇓ metabolism. So, dose must be **reduced**
      - **Chloramphenicol** may cause *gray baby syndrome in infants* due to **low** metabolizing enzymes
    - **Sex**
      - **LME in males > females**
      - **ex.** *Propranolol* and *salicylates* their metabolism in males > females
    - **Hormones**
      - Glucocorticoids & male sex hormones → **increase LME**
      - Female sex hormones → **decrease LME**
    - **Nutrition**
      - Malnutrition → **decrease LME**
  - **Genetic factors**
    - **Species difference**
    - **Individual difference**
  - **Environmental factors**
    - **Stress**
      - increase glucocorticoids → ⇑ **LME**
    - **Foreign compounds**
      - Insecticides , CCl$_4$, Carbon monoxide, O$_3$
    - **Drugs**
      - Inducers of LME
      - Inhibitors of LME

LME inhibition
- **Opposite of LME induction**
- **Effect of enzyme inhibition**
  - ⇑ **Duration** of action
  - ⇑ **Intensity** of action
  - ⇑ **Toxicity**
  - ⇓ **Tolerance**
- **Examples**
  - ***Foreign compounds***
    - CCl$_4$ - CO - Ozone (O$_3$)
  - **Drugs**
    - Cimetidine - Chloramphenicole
      - ⇓ metabolism of *warfarin* → bleeding
    - Disulfuram (antabuse)
      - **Used to treat alcoholism**
        Disulfuram *inhibits acetaldehyde dehydrogenase* enzyme → **STOP** alcohol metabolism "at the acetaldehhyde stage" → accumulation of acetaldehyde → toxicity **(Hangover)** → ⇑ heart rate + shortness of breath + flushing + visual disturbance

Take care

Some drugs produce their pharmacological effect by interfering with metabolism of other substances
- **ex. Methotrexate** → inhibit folate reductase enzyme → prevent reduction of folic acid to tetrahydrofolate (THF)
- **Anticholine esterases** → inhibit cholinesterase enzyme → accumulation of Acetylcholine
  - **So,** *the metabolizing enzymes are targets for drug action*

LME induction
- **Increase** of enzyme activity due to **increase** amount of enzyme proteins
- **LME inducers**
  - ⇑ their **OWN** metabolism
  - ⇑ metabolism of other **co-administered drugs**
- Maximum effect of LME inducers appear within **TWO weeks**
- **Effects of enzyme induction**
  - ⇓ **Duration** of drug action
  - ⇓ **Intensity** of action
  - ⇓ **Toxicity**
  - Development of **tolerance**
- **Examples**
  - ***Drugs***
    - Barbiturates
    - Phenytoin
    - Rifampicin
    - Ethanol
    - Phenylbutazone
  - ***Foreign compounds***
    - DDT - Lindane (insecticides)
    - Chlorofluorocarbons (propellents)
    - Benzopyrine - aromatic hydrocarbons (tobacco smoke)

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PHARMACOKYNETICS

- **Metabolism** ✓
- **Excretion**
- **Absorption** ✓
- **Distribution** ✓

Introduction

Excretion is the second major process by which drug activity is terminated

Elimination of a drug = Metabolism (*biotransformation*) + Excretion

Kidneys are the major site of excretion

Each kidney is composed of 2 parts : Cortex and medulla

The functional unit of excretion in the kidney is called **nephrons**
each kidney contains about 1 million nephrons

Routes of excretion

Extrarenal route

Lungs, GIT & Bile, Sweat, Saliva, Breast milk

Renal route

3 Steps

1- Glomerular filtration

Blood goes to *glomerulus* through afferent arteriole →
Filtered under high pressure in **Bowman's capsule *"ultrafilter"***
→ Then blood is discharged through efferent arterioles

Only **water** and **small molecules** and ions can pass through Bowman's capsule

Big molecules such as plasma proteins → can not pass
So, plasma proteins-bound drug *can not pass*, only free drug can

In case of nephritis (*inflammation in kidney*) → pores of glomeruli are wider
→ albumin may pass in urine → **albuminuria**

2- Passive tubular reabsorption

Passive process, occurs at proximal and distal tubules

Water and other nutrients needed by the body are normally reabsorbed from renal tubules by ***passive diffusion***

So, the concentration gradient of the drug at the end of tubules is **100 times** more than at the beginning → *due to water reabsorption*

Unionized forms of drug *(lipid soluble)* → can pass back to blood
→ Passive reabsorption according to concentration gradient

Ionized forms of drug *(lipid insoluble)* → remain in tubular fluid → excreted in urine

Ionization of drugs depend on PH of urine

- **Basic drugs** are ionized in acidic urine → more excreted
- **Acidic drugs** are ionized in alkaline urine → more excreted

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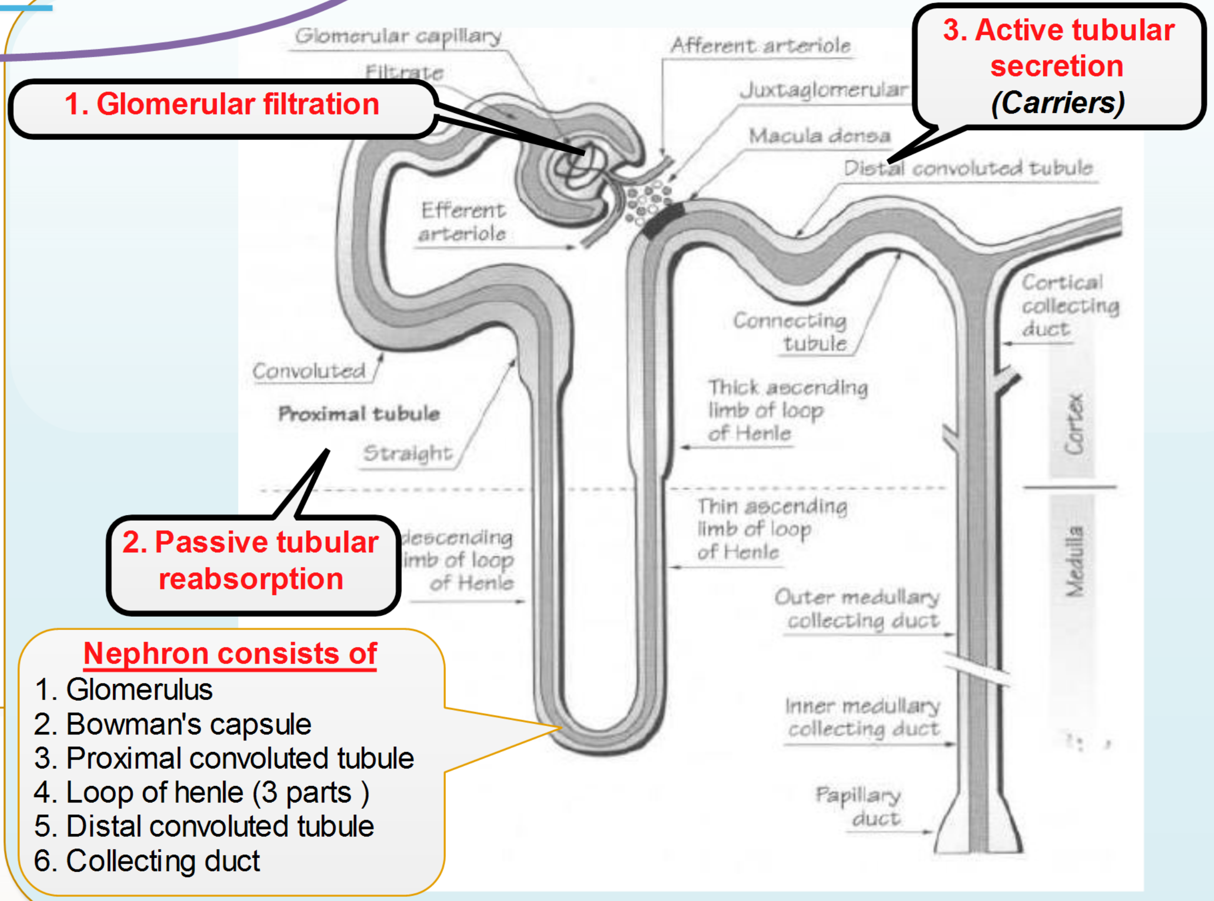
3- Active tubular secretion

Renal tubules contain transport system (carriers) used to transfer drugs *against concentration gradient* from **blood to tubular fluid**
- using active transport = carriers + energy

Transporters have *low specificity*
→ Two drugs can compete for the same transporter
→ ***decrease*** renal excretion of both drugs


Glomerular capillary
Filtrate
Afferent arteriole
Juxtaglomerular
Macula densa
Distal convoluted tubule
Efferent arteriole
Convoluted
Proximal tubule
Straight
Connecting tubule
Cortical collecting duct
Thick ascending limb of loop of Henle
Cortex
Thin ascending limb of loop of Henle
descending limb of loop of Henle
Medulla
Outer medullary collecting duct
Inner medullary collecting duct
Papillary duct
1. Glomerular filtration
2. Passive tubular reabsorption
3. Active tubular secretion (Carriers)

Nephron consists of

1. Glomerulus
2. Bowman's capsule
3. Proximal convoluted tubule
4. Loop of henle (3 parts)
5. Distal convoluted tubule
6. Collecting duct

Forced diuresis (ion trapping)

It is the enhancement of excretion of a certain drug by controlling PH of urine

Forced alkaline diuresis

Used for elimination of *weak acidic drugs* **ex. barbiturates**
through alkalinization of urine using **$NaHCO_3$** → favours ionization of acidic drugs → prevent tubular reabsorption → ⇑ elimination

Forced acidic diuresis

Used for elimination of *weak basic drugs*
ex. amphetamine , strychnine , morphine
through acidification of urine using **NH_4Cl** → favours ionization of basic drugs → prevent tubular reabsorption → ⇑ elimination

Routes of excretion

Renal route

3 Steps

Drug interactions at excretion sites

Probenicid and Penicillin (Uricosuric) (Antibiotic)
Probenicid competes with Penicillin for the carrier responsible for its secretion→ ⇓ excretion of Penicillin → prolongation of action of Penicillin

Salicylates (low dose) and Uric acid
Salicylates compete with Uric acid for the same carrier → **retention** of Uric acid → **Gout**

Salicylates and Methotrexate
Salicylates compete with Methotrexate for its anion transporter → ⇓ excretion of Methotrexate

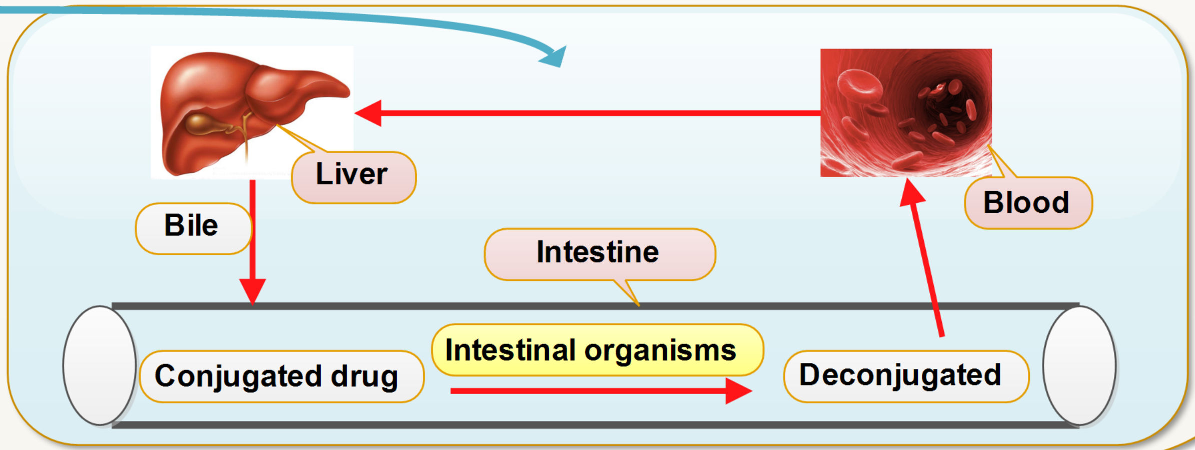
Probenicid → ⇓ uric acid
Salicylates (at low dose) → ⇑ uric acid
→ *Physiological antagonism*

Extrarenal route

Lungs
Gaseous and volatile anesthetics are excreted through Pulmonary alveolar membrane by simple diffusion

Bile
Many substances are excreted in the bile mainly as glucuronides or sulphate **(conjugated drugs)** → enters the gut → excreted in faeces

Some conjugates may be deconjugated by intestinal organisms → reabsorbed into circulation → **Enterohepatic circulation**



Breast milk
ex. Chloramphenicol - estrogen (oral contaceptives)
Undesirable side effects to nursing infants

Sweat
ex. Nicotinamide - Quinine - Sulfanilamide

Factors affecting drug dosing

Age
Child dose = Adult dose X (age in years / age+12) , *If age > 2 years*

Weight
Child dose = Adult dose X (weight in pounds / 150) , *if age < 2 years*

Sex
Sometimes females are more susceptible to drugs than males

Pathological status
Liver or kidney diseases could decrease metabolism & / or excretion of the drug

Drug combination
Summation or Addition , Synergism , Potentiation , Antagonism ***→ Already studied***

Adverse drug reactions

Side effects

These are not the main effect (unwanted) but some times are *considered as a clinical use* of the drug

VIAGRA
50mg
4 Film-Coated Tablets

ex. Atropine

- **Main effect**→ smooth muscle relaxant (anti-spasmodic)
- **Side effect**→ dryness of respiratory tract secretions and dry mouth
  →***So,*** may be used during anesthesia to decrease respiratory tract secretions
- **Side effect**→ decrease GIT motility constipation

ex. Sildenafil (Viagra®)

- Clinical trials were to use it for treatment of hypertension → but it was found that it has a useful side effect in treatment of erectile dysfunction in men → so, finally it is formulated as a drug for erectile dysfunction

Undesirable effects

These are effects that are totally unwanted (undesired)

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1- Idiosyncrasy / pharmacogenetic factors

Abnormal reaction to a drug due to genetic factors

1 - Succinylcholine apnea
→ Pseudocholinesterase deficiency

Pseudocholinesterase is an enzyme responsible for degradation of Ach and similar substances mainly in blood

Succinylcholine (similar to Ach) is a skeletal muscle relaxant used before anesthesia by dripping method (drop by drop) and is degraded in blood
In case of deficiency of the enzyme → succinylcholine is accumulated ⇑ → causing respiratory failure
Succinylcholine apnea انقطاع فى النفس

2- Malignant hyperthermia

Inherited muscle disorder → abnormal increase in Ca^{+2} release from endoplasmic reticulum

Exposure to general anesthetics (ex.isoflurane) and/or succinylcholine → fever , muscle rigidity tachycardia lactic acidosis

3- Hereditary methemoglobinemia

Deficiency of methemoglobin (MetHb) reductase enzyme which is responsible for the reduction of $\mathbf{Fe^{+3}}$ in RBC's hemoglobin to $\mathbf{Fe^{+2}}$ *to be able to carry oxygen to tissues*
→ Upon administration of oxidant drugs (ex.Nitrates) → ⇑ **MetHb** → **hypoxia and cyanosis**

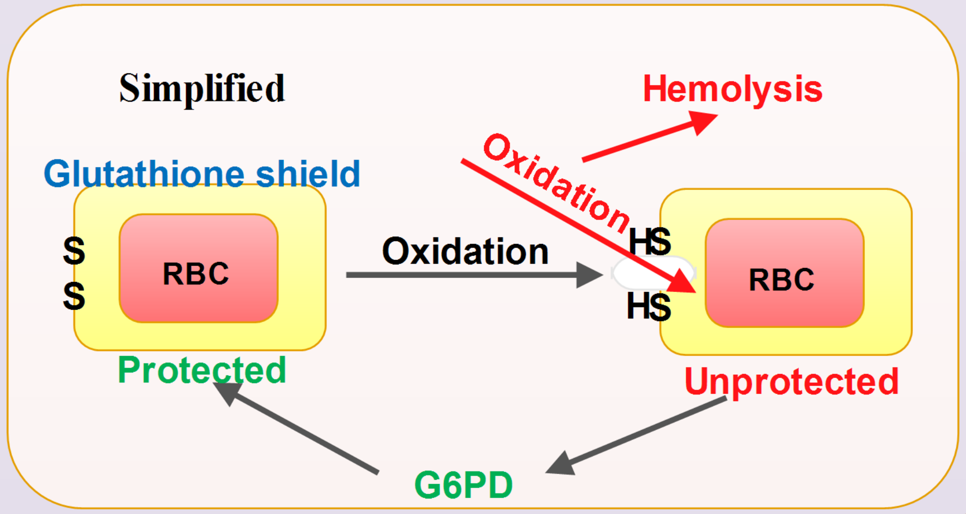
4- Acetylator phenotype

- Slow acetylators (50% of Caucasians)
- Rapid acetylators (90% of Asians)

ex. Isoniazide is metabolized by acetylation →
,**so *Slow acetylators* → *isoniazid toxicity***
1. Peripheral neuropathy (isoniazid complexes with vit B_6 → ⇓ vit B_6)
2. Bladder cancer
3. Autoimmune disorders

5- Glucose-6-phosphate dehydrogenase deficiency *"Favism"*
أنيميا الفول

G6PD enzyme is responsible for **maintaining glutathione** (molecules shielding RBCs) **in reduced form** → prevent hemolysis of RBCs
In case of enzyme deficiency , upon exposure to oxidants (ex.Nitrates , chloroquine ,**fava beans**) → that will oxidize (remove) glutathione shield → exposing RBCs to oxidants and **hemolysis**



2-Tolerance

1. Congenital tolerance

- **Racial tolerance :** Ephedrine does not produce mydriasis in Mongols
- **Species tolerance :** Histamine does not affect rabbit's intestine
- **Individual tolerance :** due to genetic variation

2. Acquired tolerance

It is decreased response to the agonist after its *repeated injection* in small doses

Drug dose must be increased to maintain a certain pharmacological effect
Occurs over a long period

Mechanisms of Hyporeactivity
Drug desensitization

1- **Change in the receptor:** Conformational change in the receptor → normal binding of agonist without opening of ion channels

2- **Down regulation (*loss of receptors*):** Prolonged exposure to **agonist** → gradual decrease in number of receptors *(receptors are taken into the cell by endocytosis)*

3- **Exhaustion of mediators**: **ex.** Depletion of catecholamines by amphetamine

4- **Liver microsomal enzyme induction**: *increase* metabolic degradation **ex.** barbiturates

3-Tachyphylaxis

Acute acquired tolerance → it is a type of tolerance that occurs very rapidly

AFRIN
Otrivin
Children

- Barium chloride in rabbit's intestine
- **Using nasal decongestants** → causes exhaustion of mediators → so lose their effects upon use for more than nearly 5 days continuously → so, advise the patient not to use the nasal decongestant for more than 4-5 days (stop it and then return after a while)

Tolerance - Tachyphylaxis - Desensitization → are called **Hyporeactivity syndromes** → **effect ⇓ upon time**

Adverse drug reactions

Undesirable effects

4-Hyper-reactivity syndrome

1- Upregulation (Hyper susceptibility)

Prolonged exposure to antagonist or **decreased** concentration of **agonist** → **Upregulation** → ⇑ number on receptors

So, *Sudden withdrawal of antagonist* → agonist will act on LARGE number of receptors → exaggerated response

ex. Sudden withdrawal of **Propranolol** (β blocker) → Severe tachycardia

→ so, advise the patient **NOT** to quit using it suddenly

It should be stopped within 7-14 days

INDERAL
tablets 40 mg
50 Tablets

2- Accumulation :

Drug effect can increase also when rate of administration > rate of metabolism or excretion

5-Drug dependence

1- Habituation

- It is emotional or psychological dependence **(psychic craving)** for a drug
- If the drug is stopped → the individual might suffer from some emotional distress for a short period of time but finally will recover

ex. Coffee , Tea , Tobacco smoking

2- Addiction

- It is **psychic craving and physical dependence** on a drug
- Through repeated administration of the drug → body tissues become accustomed to it → to the extent that they require the drug to function normally !
- If the drug is stopped → severe withdrawal symptoms / abstinence syndrome

ex. Morphine , Alcohol , Barbiturates

6- iatrogenic effect

It is drug induced complication
(the drug itself produces a disease)

Examples

- **Chlorpromazine** (antipsychotic) used to treat schizophrenia
- **During treatment** symptoms of parkinsonism develop **!!**

7-Teratogenic effect

These are fetal malformations produced by certain drugs when used during pregnancy

Examples

- **Isotretinoin** a drug used for the treatment of acne حب الشباب
- Should be stopped before getting pregnant by at least 6 months !

ISOtretinoin